II. REMARKS

Claims 47, 57, 59 to 63, 71 to 73, and 76 are pending.

A. Regarding the Amendments

A Substitute Specification is enclosed herewith, including a clean version to be entered, and marked copy showing the amendments. It is noted that the marked copy fails to show deletion of line numbering as was present in the original specification, and also fails to show the PCT application and publication numbers as in the original specification. Except for these omissions, all changes to the specification are shown in the marked version. Changes are indicated using the "Track Changes" tool of Microsoft Word, wherein deletions are indicated by strikethrough and additions are indicated by double underlining.

The specification has been amended at page 1 to insert the priority information, and throughout to insert paragraph numbering. In addition, the specification has been amended throughout to delete "underlining" that was present in the originally filed application (e.g., in referring to journal volumes), and to preserve the proprietary nature of trademarked products. The specification also has been amended to correct typographical errors, and for consistency (e.g., "mls" has been changed to "ml" to indicate milliliters). Further, the specification has been amended at paragraph 34 to insert the U.S. Patent Number for the recited patent application, and also has been amended at paragraphs 14 and 26 to insert the appropriate Sequence Identifier.

It is submitted that the amendments as set forth in the Substitute Specification merely address formalities, or correct typographical errors, and, therefore, do not add new matter. Accordingly, entry of the Substitute Specification is respectfully requested.

A Substitute Sequence Listing also has been submitted. The Substitute Sequence Listing contains sequences as originally filed in the application, and includes SEQ ID NO:7, as requested by the Examiner. As such, the Substitute Sequence Listing does not add new matter.

Claim 71 has been amended to correct a typographical error, to insert a Sequence Identifier, and to clarify the result of the claimed method by reciting the preamble. As such, the amendments merely address formalities, and do not add new matter. In addition, claim 71 has been amended to clarify that an amplification product ends "immediately preceding" a stop codon. The amendment is supported, for example, by claim 5 as originally filed and, therefore, does not add new matter.

Claim 76 has been amended to clarify that the expression vectors allow for expression of an ORF in prokaryotes and eukaryotes. The amendment merely clarifies the claim language, and does not add new matter.

B. Regarding the Declaration

It was noted in the Office Action that a change had been made to the Declaration, but that the change was not initialed and dated by the person making the change. Inventor John Heyman has indicated he made the change, and has initialed and dated the change so indicating. A copy of the Declaration, which has been initialed and dated by Inventor Heyman, is attached hereto. As such, it is respectfully requested that this objection be withdrawn.

C. Regarding the Specification

The Abstract is objected to for using the term "comprising". The Abstract has been amended to delete this term and others that may be objectionable. As such, it is requested that this objection be withdrawn.

The Specification also is objected to as allegedly using trademarked terms improperly, and failing to update the status of a copending application. The Specification has been amended to attend to these matters. As such, it is requested that these objections be withdrawn.

The Specification also is objected to because the sequence "CACCATG" in claim 1 is not contained in a Sequence Listing. Although, as discussed with the Examiner, the sequence does not contain 10 nucleotides and, therefore, is not subject to the Sequence Rules, Applicants nevertheless have submitted a Substitute Sequence Listing herewith, including a Sequence Identifier for CACCATG (SEQ ID NO:7), and have amended the specification and claims to include the Sequence Identifier. Accordingly, it is requested that this objection be withdrawn.

D. Incorporation by Reference

It is alleged in the Office Action that the attempt to incorporate a co-pending application into the application by "incorporation by reference" is improper because the application is necessary to support the claimed invention. Applicants submit, however, that the cited patent application is not essential material with respect to the claimed invention, but merely describes methods of cloning using Vaccinia topoisomerase. Such methods were well known at the time the subject application was filed, and the cited patent application was provided to exemplify methods for cloning using Vaccinia topoisomerase. As such, the cited patent application not "essential material". Nevertheless, the specification has been amended at paragraph 34 to update the citation by including the U.S. Patent Number for the cited application. As such, the objection is moot.

E. Rejections under 35 U.S.C. § 112

The objection to the specification and corresponding rejection of claims 47, 57, 59 to 63, 71 to 73 and 76 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement are respectfully traversed.

It is noted that, in a teleconference initiated by the Examiner on April 2, 2003, the Examiner indicated that claim 71 and claims depending therefrom would be allowable if the

remaining claims were cancelled. The Examiner further pointed out that claim 75 was inconsistent with the language of claim 71, in that claim 71 recited in (c) that "vaccinia DNA topoisomerase" was used, whereas claim 75 recited that the enzyme could be "vaccinia DNA topoisomerase, a lambda integrase, an FLP recombinase, or a P1-Cre protein". Upon further discussion, the Examiner agreed that claim 71 could be amended to recite the additional enzymes. In reliance on the Examiner's representation, Applicants filed an Amendment (dated April 3, 2003), amending the claims, including canceling claims, as requested. However, the Examiner reconsidered and indicated the claims would not be allowed because the sequence recited in claim 71 was not included in the Sequence Listing and, therefore, had not been searched. Throughout a series of telephone conversations with the Examiner prior to and following the filing of the Amendment dated April 3, 2003, there was no discussion or suggestion of potential issues under 35 U.S.C. § 112, first paragraph (see, also, Examiner Interview Summary regarding the Interview held 03 April 2003). As such, Applicants and Applicants' undersigned representative believed prosecution had advanced beyond this stage, and are confused by the numerous grounds of rejection under the first and second paragraphs of 35 U.S.C. § 112, particularly since none of the rejections relates to the sequence set forth in claim 71.

It is alleged in the Office Action that the specification does not teach how to use the library of expressible gene sequences produced by the claimed method. It is stated that the specification discloses that the library of expressible genes expresses different proteins, but that it is not positively stated as to whether this is the use of the library. It is further stated that, even if it is assumed that this is the use, the unpredictable effect of the genes makes it "highly likely that a particular protein or protein of interest may not be expressed by the recited library" (May 1, 2003, OA, page 5, emphasis added). It is stated, for example, that the expressed protein could

be toxic to the host cell, and that "the link between expression of the marker protein and the protein of interest can limit the expression of the protein of interest".

As an initial matter, it is noted that the claims are directed to methods of producing a "library of expressible open reading frames (ORFs)". The claims are not directed to the proteins encoded by such ORFs, and are not directed to expressing the expressible ORFs. As such, it is submitted that the issues raised with respect to the likelihood (or not) that an encoded protein may be toxic would not appear to be relevant. Nevertheless, even if, for argument sake, it is considered that a protein encoded by an expressible ORF is expressed in a cell, and if it is further assumed that the expressed protein is toxic when expressed in the cell, the skilled artisan, desiring the encoded protein, would have known that the could be expressed using an *in vitro* translation, or transcription/translation system, as such systems were well known and routinely used in the art at the time the subject application was filed. As such, it is requested that this basis of the rejection be removed.

With respect to a "marker protein", Applicants again point out, as discussed above, that the claims are not directed to expressed proteins. As such, any potential toxicity of a marker protein would not appear to be directly relevant to the claimed subject matter. Further in this respect, Applicants point out that the claims do not refer to any marker protein or sequence encoding a marker protein. As such, it is submitted that this ground of rejection is not relevant.

While, as mentioned above, it is believed that the issue raised in the Office Action with respect to the "marker protein" is not relevant, it is noted that the Examiner cites to the "Background of the Invention" section of Gillies et al. (U.S. Pat. No. 5,665,578) to support this ground of rejection. Applicants point out, however, that the '578 Patent, which issued well before the priority date of the subject application (and itself has a priority date of March 1986) is

directed to vectors and methods for overcoming such potential problems (see, e.g., Abstract). As such, the cited reference appears to solve any potential toxicity problem that may be associated with expression of a marker protein.

Eckert and Kunkel, 1991, at page 17, also is cited in support of the rejection. Eckert and Kunkel describe fidelity rates of polymerases used in PCR and describe base substitution error rates. Applicants submit, however, that Table 1 (pages 18-84) of the subject application, which provides a library of expressible human ORFs produced according to a method of the invention, demonstrates that PCR can be useful in the claimed method, despite the well known error rates associated with PCR. It is further submitted that Table 1 of the subject application provides substantial evidence that the claimed methods are enabled with respect the above-mentioned issues.

With respect to a "use" of a library produced according to a method of the invention, it is submitted that the skilled artisan would recognize that such a library is useful as a research tool, for example, to characterize RNA molecules expressed in a particular cell type. Sambrook et al., for example, recognize that cloning into prokaryotic vectors "has become a fundamental tool" of eukaryotic molecular biology (see page 8.12, of Sambrook et al., "Molecular Cloning: A laboratory manual" 2d ed. (1989 Cold Spring Harbor Laboratory Press); see, also, page 16.2, regarding cloning in mammalian cells; copies of pages 8.2 and 16.2 are attached hereto as Exhibit A).

It is also stated that the specification fails to teach how to make a library, wherein the different enzymes as recited in the claims are used to insert an amplified and purified ORF. Applicants are uncertain of the basis for this rejection, as no objective evidence is provide in support of the rejection. Further, as discussed above, Applicants' undersigned representative had

discussed with the Examiner whether claim 71 could be amended to include the enzymes, which were recited in previously pending claim 75 (see Amendment dated April 3, 2003), and believed that agreement had been reached with respect to this amendment. Nevertheless, Applicants point out that the use of the recited enzymes to link nucleic acid molecules was well known in the art prior to the time the subject application was filed (see, e.g., U.S. Pat. No. 4,959,317, describing the use of loxP-Cre to link nucleic acid molecules; U.S. Pat. No. 5,888,732 (claiming priority to at least June 1996), describing the use of lambda integrase to link nucleic acid molecules; and Ringrose et al., which, as stated by the Examiner in support of the obviousness rejection, describes "that FLP and Cre have been used extensively in a variety of organisms to engineer specific DNA rearrangement at defined sites" - May 1, 2003, OA, page 11) As such, it is submitted that undue experimentation would not have been required for the skilled artisan to use an enzyme as recited in claim 71 to insert a purified amplified ORF into an expression vector according to a method of the invention.

For the above reasons, it is submitted that one skilled in the art would have known how to practice the claimed methods without undue experimentation, and would have known how to use libraries of selected expressible ORFs produced according to such methods. Accordingly, it is respectfully requested that the objection to the specification be withdrawn and, therefore, that the rejection of claims 47, 57, 59 to 63, 71 to 73 and 76 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, be removed.

The objection to the specification and corresponding rejection of claims 47, 57, 59 to 63, 71 to 73 and 76 under 35 U.S.C. § 112, first paragraph, as allegedly lacking a written description are respectfully traversed.

It is stated in the Office Action that the specification does not support "using an enzyme" to insert the purified amplified ORFs into a vector. It is stated, for example, that the specification does not describe how the enzyme is used. Applicants submit, however, that the one skilled in the art would have known how to "use an enzyme" for a purpose as recited in the claims, particularly the recited enzymes (see, e.g., U.S. Pat. No. 4,959,317; U.S. Pat. No. 5,888,732; and Ringrose et al., as discussed above with respect to the enablement rejection). Further, Applicants point out that Paragraph 31 of the subject application describes the recited enzymes, and discloses references relevant to the enzymes (see, also, claim 11 as originally filed). As such, it is submitted that the specification clearly describes how to use an enzyme as recited in the claims and, therefore, requested that this ground of the rejection be removed.

It is further stated that the recited 5' primer (claim 71, step a) is not described in the specification (or at least is being inconsistent therewith). Citing to page 14, lines 9-10 (see Paragraph 50 of the Substitute Specification), the Examiner states that the specification "recites a template that contains ATG as the start codon and a 5' primer of SEQ ID NO:1." However, the Examiner has misread this passage, which discloses that "the templates each contain a common sequence immediately 5' of the start ATG (5'-GCA...CACC) (SEQ ID NO:1)." As such, the templates all share a common sequence, which comprises SEQ ID NO:1 positioned "immediately 5' of the start ATG". In this respect, it is noted that SEQ ID NO:1 ends (at its 3' terminus) with "CACC", which, when positioned "immediately 5' of the start ATG", generates "CACCATG", which is the sequence recited in claim 71 (SEQ ID NO:7). Thus, when "a 5' primer [comprising] 5'-CACCATG" is used for PCR according to a method of the invention, it would hybridize to the complement of the "template" as disclosed in Paragraph 50, to generate an ORF containing the CACC Kozak sequence and the ATG start site. As such, there is no inconsistency in the subject application, which clearly discloses how a 5' primer comprising

5'-CACCATG would be used to generate an ORF from a template as described in Paragraph 50. Accordingly, it is respectfully requested that this ground of the rejection be removed.

It is further stated in the Office Action that the recited 3' primer that causes amplification product to end just prior to the stop codon broadens the specification recitation of the stop codon being at the exact position (May 1, 2003, OA, page 7, lines 5-8). Applicants point out, however, that claim 5 of the application as originally filed recites "wherein...the 3' primer causes the amplification product to end at the third position of the codon immediately preceding the stop codon." Applicants submit that "the third position of the codon immediately preceding the stop codon" is "just prior to a stop codon" and, therefore, would submit that the language of claim 71 does not broaden the specification. Nevertheless, in order to advance prosecution of the subject application, claim 71 has been amended to recite the language of original claim 5. As such, it is requested that this ground of rejection be removed.

It is also stated that the specification fails to describe the high-throughput format employed, or as to what is included or excluded by such a format. However, the specification exemplifies a high throughput format in Examples 1 and 2 by the use of a 96-well plate format. In view of the exemplified high throughput format, it is submitted that one skilled in the art would have recognized that Applicants were in possession of a method that can be performed in a high throughput format, and further would have known of numerous different high throughput formats as are routinely used in the art. As such, it is requested that this ground of rejection be removed.

It also is stated that there is no description that the 5' primer will encode the different generic proteins as recited in claim 61. However, as indicated in the Amendment dated April 3, 2003, Table 1 provides the requisite evidence. More specifically, Table 1 discloses many protein

families comprising proteins encoded by the exemplified human ORFs, including, for example, families of kinases (e.g., MAP kinases, see C5 at page 20; 169-16 at page 24; and 215-38 at page 26; and c-Jun kinases, JNK, see 215-2, 169-37, 169-25, and 167-16 at pages 69-70), of phosphatases (e.g., type 2 protein phosphatases, including type 2A, see C3, M428 E1, and M478 A1 at page 31, and M316 B1 and C7 at page 35, and type 2C phosphatases, see M465 A6 at page 65), and of oncogenes (e.g., Ras related proteins, see M512 H5 at page 33, C5 at page 68, M302 B3 at page 74, C1 at page 75, and M312 F3 at page 78).

Numerous additional families of proteins are evident upon inspection of Table 1, including, for example, families of growth factors (e.g., bone morphogenic proteins, see E2 at page 33, M316 B1 at page 35, and H4 at page 39), of G protein coupled receptors (e.g., D2 at page 19, 215-25 at page 28, 166-64, 166-88 and 166-76 at page 69, and M423 E5 at page 70), of heat shock proteins (e.g., M365 E4 at page 44, and M371 F4 at page 52) and of ribosomal proteins (e.g., M22 D4, M314 E2, M266 F5, etc., at page 67). Applicants point out that the proteins exemplified in the above list for the various families are not exhaustive for each of the families, and that the exemplified families are only a fraction of the total families disclosed in Table 1, including families comprising more closely related members as well as families comprising more distantly related members. As such, it is submitted that the subject matter of claim 61 is fully supported by the subject application.

For the reasons set forth above, it is submitted that the subject application clearly describes and fully supports the claimed methods. Accordingly, it is respectfully requested that the objection to the specification be withdrawn, and that the corresponding rejection of the claims under 35 U.S.C. § 112, first paragraph, as allegedly lacking a written description be removed.

The rejections of claims 47, 57, 59 to 63, 71 to 73 and 76 under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite are respectfully traversed.

It is alleged in the Office Action that the preamble of claim 71 recites "a library", which is at odds with the recitation of "a plurality". However, the preamble refers to "a library of selected expressible [ORFs]", whereas claim 71 a) refers to "a plurality of ORFs". Applicants point out that "selected expressible ORFs" are not obtained until step e), which is the "selecting" step. As such, the subject matter is clear when considered in the context of the entire claim.

It also is stated that the preamble recites "producing a library", whereas the body of the claim recites "selecting transformed cells comprising ORFs". Applicants point out, however, that "cells" is plural (i.e., more than one), and each selected cell contains an expression vector comprising the amplified ORFs. As such, the selected cells comprise a "library", and the steps as set forth in claim 71 result in "producing a library". Nevertheless, claim 71 has been amended to clarify that the method produces a library. As such, this rejection is moot.

It also is stated the "orientation" is not clear within the claimed context. however, the context is "expression vectors comprising ORFs in an orientation for expression of a polypeptide". It is submitted that the skilled artisan would know that such an orientation would be with respect to promoter elements present in an expression vector. As such, it is requested that this rejection be removed, or that it be clarified as to what specifically is unclear.

It also is stated that the term "expressible" connotes uncertainty as to whether said ORF was indeed expressed. As discussed above, the claims do not require that the ORFs be expressed, only that they are contained "in expression vectors in an orientation for expression". Thus, the term "expressible" means that the ORFs can be expressed. Accordingly, absent

objective evidence that one skilled in the art reading the claims would not know the meaning of "expressible", it is requested that this ground of rejection be removed.

It also is stated that "to end just prior to a stop codon" is not clear. The claim has been amended to recite "immediately preceding a stop codon." It is submitted that "immediately preceding" would be clear to the skilled artisan and, therefore, requested that this ground of the rejection be removed.

It is alleged that claim 76 is unclear because the term "suitable" is indefinite as to vectors or factors and/or conditions considered suitable for prokaryotic and eukaryotic expression vectors. Claim 76 has been amended to clarify the claimed subject matter. As such, it is requested that this rejection be removed.

It is alleged that claim 61 is at odds with the disclosure in reciting a specific primer is required for each expressible gene. Applicants point out, however, that the single primer as set forth in claim 71 was used to obtain ORFs for the families of proteins as recited in claim 61 (see Table 1; see, also, discussion above regarding "written description"). As such, claim 61 is directed to a subset of the library of expressible ORFs produced by a method of the invention, and does not require a specific primer for each expressible ORF. Accordingly, it is requested that this ground of rejection be removed.

In view of the amendments and for the reasons set forth above, it is submitted that one skilled in the art, reading the claims, would know the subject matter regarded as the invention. Accordingly, it is respectfully requested that the rejections of claims 47, 57, 59 to 63, 71 to 73 and 76 under 35 U.S.C. § 112, second paragraph, be removed.

F. Prior Art Rejection

It is noted that a rejection under 35 U.S.C. § 103(a) was made in the Office Action mailed May 1, 2003, and that a second such rejection was made in the Supplemental Office Action mailed July 7, 2003. For completeness, both rejections are addressed.

The rejection of claims 47, 57, 59 to 63, 71 to 73 and 76 under 35 U.S.C. § 103(a) as allegedly obvious over Harney (U.S. Pat. No. 6,277,632), in view of Shuman (U.S. Pat. No. 5,766,891) or Ringrose et al., as set forth in the May 1, 2003, Office Action is respectfully traversed.

It is stated in the Office Action that Harney describes methods for ligating nucleic acid molecules using a ligase, that Shuman describes advantages of using a topoisomerase as compared to a ligase, and that Ringrose et al. describe the use of FLP and Cre to engineer specific DNA rearrangement at defined sites. It is alleged that the claimed methods would have been obvious because one of ordinary skill would have been motivated to substitute the ligase of Harney with the topoisomerase, FLP or Cre system because of the advantages of these enzymes as described by Shuman and by Ringrose et al.

Applicants point out, however, that the cited references, either alone or in combination, do not teach or suggest amplifying DNA using a primer pair including a 5' primer comprising a nucleotide sequence starting 5'-CACCATG and a 3' primer, which causes the amplification product to end immediately preceding a stop codon, as required by the claims. As such, it is submitted that claimed methods would not have been obvious in view of the cited references and, therefore, is respectfully requested that this rejection of the claims under 35 U.S.C. § 103(a) be removed.

The rejection of claims 47, 57, 59 to 63, 71 to 73 and 76 under 35 U.S.C. § 103(a) as allegedly obvious over Harney (U.S. Pat. No. 6,277,632), in view of Shuman (U.S. Pat. No. 5,766,891) or Ringrose et al. and Dubensky et al. (U.S. Pat. No. 6,342,372), as set forth in the July 7, 2003, Office Action is respectfully traversed.

The Harney, Shuman, and Ringrose et al. references are applied as described above. Dubensky et al. is applied as describing a primer comprising CACCATG. It is alleged that the claimed methods would have been obvious because one of ordinary skill would have been motivated to substitute the ligase of Harney with the topoisomerase, FLP or Cre system because of the advantages of these enzymes as described by Shuman and by Ringrose et al., and to further use a primer comprising the CACCATG sequence because the Kozak sequence provides for efficient translation as described by Dubensky.

Applicants point out, however, that the cited references, either alone or in combination, do not teach or suggest amplifying DNA using a primer pair including a 5' primer comprising a nucleotide sequence starting 5'-CACCATG and a 3' primer, which causes the amplification product to end immediately preceding a stop codon, as required by the claims. As such, it is submitted that claimed methods would not have been obvious in view of the cited references and, therefore, is respectfully requested that this rejection of the claims under 35 U.S.C. § 103(a) be removed.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. Although no fee is believed to be necessary in connection with the filing of this Amendment, the Examiner is authorized to charge Deposit Account No. 50-1355 if any fee is required.

The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Respectfully submitted,

Date: December 8, 2003

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Enclosure: Exhibit A